Image AF/1632

PATENT
Customer No. 22,852
Attorney Docket No. 03804.0114-02000

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
Jacques MALLET et al.	Group Art Unit: 1632
Application No.: 09/578,453	Examiner: Ram R. Shukla
Filed: May 26, 2000	
For: PHARMACEUTICAL COMPOSITIONS AND UTILIZATION THEREOF PARTICULARLY FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES	

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TRANSMITTAL OF APPEAL BRIEF (37 C.F.R. 1.192)

Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on November 13, 2003.

This application is on behalf of

☐ Small Entity ☒ Large Entity

Pursuant to 37 C.F.R. 1.17(c), the fee for filing the Appeal Brief is:

☐ $165.00 (Small Entity)

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Extension Fee (if any)	$420.00
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☒ Enclosed is a check for $750.00 to cover the above fees.

PETITION FOR EXTENSION. Appellants hereby petition for a two-month extension of time to file this Appeal Brief. If any additional extension of time is necessary for the filing of this Appeal Brief, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to our Deposit Account No. 06-0916. A duplicate copy of this paper is enclosed for use in charging the deposit account.

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 24, 2004

By: _____
William L. Strauss
Reg. No. 47,114

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Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Appellants hereby appeal to the Board of Patent Appeals and Interferences ("the Board") from the decisions of the Examiner dated May 15, 2003, and September 26, 2003, finally rejecting claims 16-26. The appealed claims are set forth in the attached Appendix. By virtue of the Notice of Appeal filed November 13, 2003, and the Petition for a Two-Month Extension of Time filed herewith, this brief is timely filed.

Three copies of this Appeal Brief are being filed, along with the fee of $330.00 required under 37 C.F.R. § 1.17(f). Please charge any additional required fees to Deposit Account No. 06-0916.

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I. Real Party In Interest

The real party in interest is Aventis Pharma S.A.

II. Related Appeals and Interferences

The Appellants, the undersigned, and the assignee are not aware of any other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. Status of Claims

The pending application was filed on May 26, 2000, as a continuation of U.S. Application No. 08/624,469 filed May 10, 1996, now abandoned, which was the national stage of PCT/FR94/01142 filed September 29, 1994. The application claims benefit under 35 U.S.C. § 119 of French Patent Application No. 93-11774 filed October 4, 1993. Appellants filed a preliminary amendment canceling claims 1-15 and adding claims 16-31. In response to the Restriction Requirement mailed October 2, 2001, Appellants elected claims 16-26.[1] These claims were rejected in the Office Action mailed November 19, 2002. That rejection was made final in the Office Action mailed May 15, 2003.

In summary, claims 27-31 have been withdrawn from consideration. Claims 16-26 have been finally rejected and are on appeal. No claim is allowed.

IV. Status Of Amendments

Appellants' most recent amendment, which was filed on February 19, 2003, has been entered.

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[1] The Restriction Requirement initially required Appellants to elect one of four groups. *See* Restriction Requirement mailed October 2, 2001, at 2. After Appellants' Petition for Withdrawal of Restriction Requirement filed August 9, 2002, was granted, the Examiner joined the claims of Groups I-III into a single group containing claims 16-26. *See* Office Action mailed November 19, 2002, at 2.

V. Summary of Invention

The rejected claims are drawn to recombinant viruses and to methods of using these viruses to inhibit p53 protein-mediated toxicity in cultured neuronal cells. The recombinant viruses of the invention may be derived from adenovirus (claims 16 and 17), adeno-associated virus (claim 16), or herpes virus (claim 16) vectors. *See* Specification at 7, lines 6-12. In certain embodiments of the invention (claim 20), the recombinant viruses are replication-defective. *See id.* at 8, lines 9-12. According to claim 16, the recombinant viruses of the invention comprise nucleic acids that 1) encode mutant p53 proteins that inhibit the activity of wild-type p53 protein, *see id.* at 4, lines 17-27; 2) contain the DNA binding site for p53 protein, *see id.* at 5, lines 3-7; or 3) encode antisense p53 RNA, *see id.* at 4, lines 4-7. In certain embodiments, the recombinant viruses of the invention comprise two of these nucleic acids (claim 19). *See id.* at 7, lines 2-5. In one embodiment of the invention (claim 18), the recombinant viruses comprise a p53 binding site with sequence SEQ ID NO: 2. *See id.* at 5, lines 14-19. In another embodiment of the invention (claim 21), the recombinant viruses comprise a p53 mutant protein named p53Val135. *See id.* at 4, lines 25-27.

According to claim 22, the methods of the invention comprise administering to cultured neuronal cells a nucleic acid that 1) encodes mutant p53 protein that inhibits the activity of wild-type p53 protein, *see id.* at 4, lines 17-27; 2) contains the DNA binding site for p53 protein, *see id.* at 5, lines 3-7; or 3) encodes antisense p53 RNA, *see id.* at 4, lines 4-7. In certain embodiments, the nucleic acid is an antisense oligonucleotide (claim 22), which may have sequence SEQ ID NO: 1 (claim 23). *See id.* at 6, lines 3-11. In certain methods of the invention (claim 25), the nucleic acid is within

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a vector. *See id.* at 6, lines 24-25. The vector may be a replication-defective virus (claim 26). *See id.*, at 8, lines 9-12.

VI. Issues

This appeal presents three issues:

1. Whether claims 16, 17, 19, 20-22, 25, and 26 patentable over Michalovitz *et al.* (*Cell*, 62:671-680, 1991) in view of Moberg *et al.* (*J. Cell. Biochem.*, 49:208-215, 1992) and Le Gal La Salle *et al.* (*Science*, 259:988-990, 1993)?

2. Whether claims 16-20, 22, 23, 25, and 26 patentable over Levrero *et al.* (*Gene*, 101:195-202, 1991) taken with Michalovitz *et al.* (*J. Cell. Biochem.*, 45:22-29, 1991) and Funk *et al.* (*Mol. Cell. Biol.*, 12:2866-2871, 1992), and further in view of Chopp *et al.* (*Biochem. Biophys. Res. Comm.*, 182:1201-1207, 1992)?

3. Whether claims 22-26 patentable over U.S. Patent No. 5,087,617 taken with Soussi *et al.* (*Nucl. Acids Res.*, 16:11384, 1988), and further in view of Chopp *et al.* (*Biochem. Biophys. Res. Comm.*, 182:1201-1207, 1992)?

VII. Grouping Of Claims

The rejected claims can be divided into two groups and do not stand or fall together. Claims 16-21 are drawn to a composition of matter: a recombinant virus. Claims 16-21 stand or fall together. In contrast, claims 22-26 are drawn to a method of using a nucleic acid to inhibit toxicity in cultured neuronal cells. Claims 22-26 stand or fall together. Although the method of claims 22-26 may use a recombinant virus, e.g., as recited by claims 16-21, composition of matter claims 16-21 could be found unpatentable over the references cited by the Examiner, while those same references might not render obvious a particular method for using the composition, in this case inhibiting toxicity in cultured neurons.

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VIII. **Argument**

Claims 16, 17, 19-22, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Michalovitz *et al.* (*Cell*, 62:671-690, 1991, Michalovitz 1") in view of Moberg *et al.* (*J. Cell. Biochem.*, 49:208-215, 1992) and Le Gal La Salle *et al.* (*Science*, 259:988-990, 1993). *See* Final Office Action mailed May 15, 2003, at 2.

Claims 16-20, 22, 23, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Levrero *et al.* (*Gene*, 101:195-202, 1991) taken with Michalovitz *et al.* (*J. Cell. Biochem.*, 45:22-29, 1991, "Michalovitz 2") and Funk *et al.* (*Mol. Cell. Biol.*, 12:2866-2871, 1992), and further in view of Chopp *et al.* (*Biochem. Biophys. Res. Comm.*, 182:1201-1207, 1992). *See id.* at 3.

Finally, claims 22-26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,087,617 to Smith taken with Soussi *et al.* (*Nucl. Acids Res.*, 16:11384, 1988), and further in view of Chopp. *See id.* at 4.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three basic criteria. First, the Examiner must point to some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. M.P.E.P. § 2143.

The Federal Circuit has held that evidence of a teaching, suggestion, or motivation to combine may flow from the references themselves, from the knowledge of one of ordinary skill in the art, or from the nature of the problem, but may not flow from Applicant's disclosure. *See Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d

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1568, 1573 (Fed. Cir. 1996), *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d (BNA) 1438, 1442 (Fed. Cir. 1991). Moreover, the evidence of a teaching, suggestion, or motivation to combine must be "clear and particular." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d (BNA) 1614, 1617 (Fed Cir. 1999).

A. The Claims Are Patentable Over the Combination of Michalovitz 1 with Moberg and Le Gal La Salle

In the final Office Action mailed May 15, 2003, the Examiner maintained the rejection of claims 16, 17, 19-22, 25, and 26 under U.S.C. § 103(a) as allegedly being unpatentable over Michalovitz 1 in view of Moberg and Le Gal La Salle. *See* Final Office Action at 2. According to the Examiner, Michalovitz 1 teaches "a temperature sensitive mutant p53val123 [sic, p53val135] that suppresses transformation at 32.5 degrees celcius [sic, Celsius]." *Id.*, page 3. Also according to the Examiner, Moberg reports that transcription from the *c-myc* promoter is inhibited by wild-type p53. *See id.* Finally, the Examiner asserts that Le Gal La Salle reports the use of adenoviral vectors to transfer genes into brain. *See id.* According to the Examiner, the motivation to make a recombinant virus comprising a mutant p53 gene is provided by Michalovitz 1, which reports the use mutant p53 to inhibit the expression of wild-type p53, and by Le Gal La Salle, which reports the use of adenoviral vectors for transferring genes into brain cells. *See id.*

Appellants traverse. Claims 16 and 22 are the only independent claims in the rejected group. Because claims 16 and 22 are not obvious over Michalovitz 1 in view of Moberg and Le Gal La Salle, claims 17, 19, 20, 21, 25, and 26, which depend therefrom are also patentable over this combination of references.

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1. Claim 16 Is Not Obvious Over the Combination of Michalovitz 1 with Moberg and Le Gal La Salle

Claim 16 recites, *inter alia*, a recombinant adenovirus comprising a nucleic acid selected from the following Markush group:

> (a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;
>
> (b) the site for binding of p53 to DNA; and
>
> (c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

According to the Examiner, the motivation to make a recombinant virus comprising a mutant p53 gene is provided by Michalovitz 1, which allegedly reports the use of a mutant p53 to inhibit the expression of wild-type p53. *See* Office Action mailed November 19, 2002, at 2. The Examiner asserts: "Michalovitz et al. [discloses] a nucleic acid that encodes a mutated p53 which inhibits transformation." Final Office Action mailed May 15, 2003, at 3.

This mischaracterizes the reference. In fact, Michalovitz 1 discloses that p53 protein exhibiting a mutant phenotype actually transforms cells, while p53 protein with a wild-type phenotype, including unmutated p53, inhibits transformation. This teaching is exactly opposite to the conclusion drawn by the Examiner.

Michalovitz 1 describes the effects of a temperature-sensitive mutant p53 protein on rat embryo fibroblast (REF) cells. *See* Abstract ("We now describe the temperature-sensitive behavior of a particular mutant, p53val135."). A temperature-sensitive mutant is "[a] conditional mutation that produces the mutant phenotype in one (restrictive or non-permissive) temperature range and the wild-type phenotype in another (permissive)

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temperature range." *See* http://www.biochem.northwestern.edu/holmgren/Glossary/Definitions/Def-T/temp-sensitive_mutation.html.

The temperature-sensitive mutant described in Michalovitz 1 (p53val135) exhibits a "mutant" phenotype at 37.5°C. *See* Michalovitz 1 at 677 ("At 37.5°C . . . it behaves like other mutants described here and in earlier work"). At 37.5°C, p53val135, *acting as a mutant*, transforms REF cells. *See id.*, Abstract ("It can elicit transformation at 37.5°C.").

At 32.5°C, p53val135 behaves "like authentic wt p53." *Id.* at 673 ("these results strongly suggested that p53val135 is indeed a ts [temperature-sensitive] mutant of p53, possessing wt [wild-type] activity at 32.5°C"). At 32.5°C, p53val135, *acting as the wild-type protein*, does *not* transform REF cells. *See id.* at 677 ("it has absolutely no transforming activity at 32.5°C"). Instead, like normal wild-type p53, the p53val135 protein suppresses cell transformation at 32.5°C. *See* Michalovitz 1 at 673 ("the inclusion of a p53val135 plasmid in a *myc* + *ras* transfection greatly eliminated focus formation at 32.5°C").

Given the disclosure of Michalovitz 1, one of ordinary skill in the art would conclude that a recombinant virus according to claim 16 "encoding a mutated form of p53" would *transform* cells, not suppress transformation as the Examiner contends. Although one of ordinary skill in the art *could* insert the mutant p53 gene of Michalovitz 1 into an adenoviral vector according to Le Gal La Salle, the Examiner has pointed to no

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motivation in the references or elsewhere to make that oncogenic (i.e., cancer-causing) virus, rather than simply use the plasmid construct disclosed by Michalovitz 1.[2]

Moreover, Michalovitz 1 neither teaches nor suggests that p53val135 or any other mutant p53 "antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*" as recited by claim 16. Nor does Michalovitz 1 teach or suggest 1) "the site for binding of p53 to DNA" or 2) "nucleic acids encoding an antisense RNA which inhibits expression of p53" as recited by claim 16. Instead, Michalovitz 1 discloses simply that p53val135 behaves like wild-type p53 at 32.5°C, but behaves like mutant p53 at 37.5°C to transform cells. This property is unrelated to the invention of claim 16.

With regard to Moberg, the Examiner asserts "contrary to Applicants[']arguments, Moberg teaches inhibition of [the] c-myc promoter by wild type p53 and its teaching is that [the] c-myc promoter is responsive to p53 regulation." Final Office Action at 3. But the Examiner's statement is not "contrary to Applicants[']arguments." It's simply less accurate than those arguments.

---

[2] The Examiner states, "Applicants[']arguments that nothing in the prior art suggests the desirability of making an oncogenic adenovirus using mutant p53 is not persusasive [sic, persuasive] because the claimed invention is not to any oncogenic adenovirus but to a recombinant virus or adenovirus that comprises a nucleic acid encoding a mutant form of p53 which antagonizes the effects of wild type p53." Final Office Action at 3. First, Appellants note that claim 16 is directed, *inter alia*, to a virus comprising "nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*." This is distinctly different from the Examiner's much broader mischaracterization of "a nucleic acid encoding a mutant form of p53 which antagonizes" *any* "effects of wild type p53." Moreover, the references relied on by the Examiner disclose only that mutant p53 is oncogenic (except for p53val135, which at the 32.5°C behaves like wild-type p53). Therefore, one skilled in the art, based on the references of record, would expect that a virus comprising a nucleic acid encoding a mutant p53 protein would be an oncogenic virus. The Examiner has pointed to no teaching or suggestion that would motivate one to make such a virus.

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As Appellants have acknowledged, "Moberg reported that wild-type p53 inhibited transcription from the c-myc promoter." Amendment filed February 19, 2003, at 4. However, as Appellants also noted, Moberg teaches that *mutant p53 had no effect* on transcription from the c-myc promoter. *See id.* Thus, Moberg discloses that the c-myc promoter is responsive to *wild-type but not mutant* p53 regulation. However, it is mutant p53, not wild-type 53, that is the subject of the instant invention. The Examiner has not explained why Moberg's disclosure would motivate anyone to use mutant p53 for anything, when mutant p53 had no effect in Moberg's system.

Finally, the Examiner asserts that Le Gal La Salle teaches the "use of adenoviral vectors for transferring [a] gene in[to] brain both in vitro and in vivo." Final Office Action at 3. According to the Examiner, the motivation for combining Michalovitz 1 with Moberg and Le Gal La Salle "was to use p53 mutant for inhibiting expression of wild type p53." *Id.*

But none of these references discloses that mutant p53 inhibits the expression of wild-type p53. As discussed above, Michalovitz 1 reports that, while exhibiting a wild-type phenotype at 32.5°C, a temperature-sensitive p53 mutant inhibits transformation of REF cells by a combination of two oncogenes, *ras* and *myc*. Michalovitz 1 says *nothing* about the effect of p53val135 on the expression of wild-type p53. Likewise, Moberg reports that wild-type p53 inhibits transcription from the c-myc promoter. Mutant p53 had no effect, and Moberg too says *nothing* about the effect of p53val135 on the expression of wild-type p53. Finally, Le Gal La Salle has nothing to do with either wild-type or mutant p53. Rather Le Gal La Salle simply reports that brain cells can be

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transfected using adenoviruses. Thus, the Examiner's "motivation" for making the proposed combination has no factual foundation in the record.

Based on Michalovitz 1, one of ordinary skill in the art would predict that an adenovirus encoding the mutant p53val135 protein would cause cancer. Based on Moberg, one of ordinary skill in the art would predict that this virus would have no utility. Because the Examiner has pointed to nothing that would motivate one skilled in the art to make viral vectors that are either oncogenic or lack utility, the Examiner has failed to make a *prima facie* case that the invention claimed in claim 16 (and claims 17, 19, 20, and 21, which depend therefrom) is obvious. Appellants request the withdrawal of the rejection of these claims under 35 U.S.C. 103(a).

2. Claim 22 Is Not Obvious Over the Combination of Michalovitz 1 with Moberg and Le Gal La Salle

Claim 22 recites a "method for inhibiting toxicity in cultured neuronal cells" using a nucleic acid selected from the Markush group of claim 16. It is clear that neither Michalovitz 1 nor Moberg nor Le Gal La Salle teaches or suggests that mutant p53, p53 binding sites, or antisense p53 RNA might be useful for inhibiting toxicity in cultured nerve cells. As discussed above, Michalovitz 1 discloses that p53val135 behaves like a mutant p53 protein to transform fibroblasts at 37.5°C and behaves like a wild-type p53 protein to suppress transformation at 32.5°C. Moberg reports that wild-type p53 suppresses transcription from the c-myc promoter, while mutant p53 has no effect. The findings of Le Gal La Salle are unrelated to p53. Because the cited references neither teach nor suggest the claimed method, Appellants request the withdrawal of the rejection of claim 22 (and claims 25-26, which depend therefrom) under 35 U.S.C. § 103(a).

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B. The Claims Are Patentable Over the Combination of Levrero with Michalovitz 2, Funk, and Chopp

The Examiner also maintained the rejection of claims 16-20, 22, 23, 25, and 26 under U.S.C. § 103(a) as allegedly being unpatentable over Levrero taken with Michalovitz 2[3] and Funk, and further in view of Chopp. Final Office Action at 3. According to the Examiner, Levrero discloses a defective recombinant adenovirus into which the hepatitis B virus *s* gene or the chloramphenicol acetyltransferase gene has been inserted. *See* Office Action mailed November 19, 2002, at 4. The Examiner further asserts that Michalovitz 2 discloses mutated mouse p53 cDNAs and the ability of mutated p53 to interfere with the function of wild-type p53. *See id.* According to the Office, Funk discloses a DNA binding site for p53 with sequence SEQ ID NO:2. *See id.* The Examiner contends that "[t]he application of these nucleic acids to p53 expression is relevant due to the association of p53 with severe ischemic cell damage disclosed by Chopp et al." *Id.*

Appellants traverse. As above, claims 16 and 22 are the only independent claims in the rejected group. Because claims 16 and 22 are not obvious over Levrero taken with Michalovitz 2 and Funk further in view of Chopp, claims 17-20, 23, 25, and 26, which depend therefrom, are also patentable over this combination of references.

1. Claim 16 Is Not Obvious Over the Combination of Levrero with Michalovitz 2, Funk, and Chopp

Claim 16 recites, *inter alia*, a recombinant adenovirus comprising a nucleic acid selected from the following Markush group:

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[3] In making this rejection, the Examiner refers simply to "Michalovitz." However, in the Office Action mailed November 19, 2002, the Examiner relied on two Michalovitz references. For purposes of this brief, Appellants assume that he intended to rely on the same two references in the final Office Action.

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

Levrero reports that a replication defective adenovirus transfects a variety of cell lines. *See* Abstract ("The recombinant viruses . . . were used to infect a wide spectrum of cells of different origin."); *see also* page 199, Table I. As is the case for Le Gal La Salle (see above), the findings of Levrero are unrelated to p53.

Michalovitz 2 is a review article concerning various mutant p53's. In contrast to Michalovitz 1, Michalovitz 2 does report that a mutant p53 protein may "act[ ] in a dominant negative fashion and [ ] effectively block[ ] the function of its wt counterpart." Page 25, left col. However, Michalovitz 2 discloses that p53 mutants of this type are oncogenic. Like Michalovitz 1, Michalovitz 2 neither teaches nor suggests that dominant negative p53 mutants have any effect on wild-type p53-mediated neuronal cell degeneration. Nor has the Examiner pointed to any evidence that one skilled in the art at the time Appellants made their invention would have reasonably expected that, simply because a p53 mutant might act by antagonizing the tumor suppressing activity of wild-type p53, that same mutant protein would antagonize wild-type p53-mediated neuronal cell degeneration. Again, both Michalovitz references report that mutant p53 proteins transform cells and disclose nothing concerning a possible role for mutant p53 proteins in neuronal cell death.

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The Examiner responds that "the claims directed to the vectors do not recite any such limitations." Final Office Action at 3-4. But, in fact, they do. Claim 16 (and claims 17, 19 and 20, which depend therefrom) specifically requires that, for those viruses comprising a nucleic acid encoding a mutated form of p53, the encoded mutant protein must "antagonize wild-type p53-mediated neuronal cell degeneration *in vitro*." In the absence of a teaching or suggestion that mutant p53 protein can perform this function, one skilled in the art would expect that a virus comprising a nucleic acid encoding a mutant p53 protein would be an oncogenic virus. As Appellants have repeatedly stated, the Examiner has pointed to no teaching or suggestion that would motivate one to make such a virus. *See, e.g.,* Amendment filed February 19, 2003, at 6.

Funk adds nothing to the combination of Levrero and Michalovitz 2. Funk discloses a DNA binding site for p53 protein complexes. *See* Title. According to the Examiner, Funk's disclosure of a binding site identical to SEQ ID NO: 2, renders obvious a virus comprising that binding site. Final Office Action at 4. Funk does not, however, teach or suggest that DNA binding sites for p53 protein complexes should be incorporated into viruses. Moreover, the Examiner has pointed to nothing that would motivate one of ordinary skill in the art to make viruses comprising a DNA binding site for p53 as recited by claim 16. In fact, none of the references of record suggest that such viruses would be useful for any purpose. The simple fact that SEQ ID NO: 2 was disclosed by Funk does not render obvious claims to recombinant viruses comprising SEQ ID NO:2.

Finally, the Examiner relies on Chopp. Chopp reports that p53 is expressed in regions of neuronal necrosis after middle cerebral artery occlusion in the rat. *See*

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Abstract. According to Chopp, "[t]he data suggest that the presence of p53 is associated with cell death and that hsp[heat shock protein]72 may regulate p53 function." *Id.* While this may suggest that hsp72 might be used to antagonize the role, if any, of p53 in neuronal cell death, Chopp neither teaches nor suggests anything regarding mutant p53, p53 binding sites, or p53 antisense RNA.

The Examiner asserts, however:

> [a]gain Applicants['] arguments that there is not evidence of record to suggest that p53 mutants or binding sites with effects on oncogenesis would have any effect on wild type p53 on cell death is not persuasive because Michalovitz taught that [a] p53 mutant inhibited transformation and Applicants have not provided any evidence why the mutant will not have [an] effect on cell death in view of the results of Michalovitz, Chopp, Funk and Levaro [sic, Levrero]."

Final Office Action at 4.

Appellants reiterate their position regarding the Michalovitz references:

1. Michalovitz 1 discloses that wild-type p53 (i.e., p53val135 at 32.5°C) suppresses transformation by a combination of oncogenes entirely unrelated to the instant invention; and
2. Michalovitz 2 discloses that some p53 mutants behave as dominant negative oncogenes;

There is ***no*** teaching in either Michalovitz reference that a p53 mutant ***behaving as a p53 mutant*** inhibits transformation. Instead, these references simply disclose that a temperature-sensitive p53 mutant, ***behaving as wild-type p53 at 32.5°C***, inhibits transformation.

Moreover, the Examiner appears to confuse the respective burdens on each party in making and traversing a *prima facie* case of obviousness. In contrast to the

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Examiner's position, Appellants do not bear the burden or introducing evidence showing "why the mutant will not have [an] effect on cell death in view of the results of Michalovitz, Chopp, Funk and Levrero." Rather, it is the Examiner's burden to introduce evidence showing that one of ordinary skill in the art would reasonably expect success in using mutant p53 protein to antagonize neuronal cell death following ischemia. *See* M.P.E.P. § 2143.01. Here, that evidence is missing. The Examiner simply points (incorrectly) to Michalovitz as evidence that mutant p53 protein suppresses transformation by oncogenes and concludes that mutant p53 protein must also suppress neuronal cell death.[4] The art of record provides no connection between these cellular events and therefore provides no motivation to combine the references in the manner proposed by the Examiner. Again, the Examiner has failed to make a *prima facie* case of obviousness.

Because the cited references neither teach nor suggest the claimed recombinant virus, Appellants request the withdrawal of the rejection of claim 16 (and claims 17-20, which depend therefrom) under 35 U.S.C. § 103(a).

2. Claim 22 Is Not Obvious Over the Combination of Levrero with Michalovitz 2, Funk, and Chopp

Claim 22 recites a "method of inhibiting toxicity in cultured neuronal cells" using a nucleic acid selected from the Markush group of claim 16. It is clear that neither Levrero nor Michalovitz 2 nor Funk teaches or suggests that mutant p53, p53 binding sites, or antisense p53 RNA might be useful for inhibiting toxicity in cultured nerve cells. Appellants again note that Chopp does not disclose that p53 causes neuronal cell death in ischemic brain. *See* Amendment filed February 19, 2003, at 6-7. Moreover, Chopp

[4] This conclusion is unjustified even if one were to conclude from Chopp that the expression of wild-type p53 was the cause of neuronal cell death in ischemic brain.

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does not disclose that antagonizing the effects of p53 would prevent neuronal cell death in ischemic brain. Chopp simply reports that p53 levels are elevated in necrotic brain regions following ischemia. *See* Abstract. Assuming, *arguendo*, that Chopp would lead one of ordinary skill in the art to believe that increased p53 levels play any role in neuronal cell death, that role could as readily be either 1) as a cause of cell death or 2) as a protective response to ischemia. In either case, the combination of Levrero, Michalovitz 2, and Funk neither teaches nor suggests the use of p53 mutants, p53 binding sites, or antisense p53 RNA (regardless of any possible role in blocking transformation) to prevent neuronal cell death. Because the cited references neither teach nor suggest the claimed method, Appellants request the withdrawal of the rejection of claim 22 (and claims 23 25, and 26, which depend therefrom) under 35 U.S.C. § 103(a).

C. Claims 22-26 Are Patentable Over the Combination of Smith with Soussi and Chopp

Finally, the Examiner maintains the rejection of claims 22-26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Smith taken with Soussi, and further in view of Chopp. *See* Final Office Action at 4. According to the Examiner, "it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the method of Smith by administering a p53 antisense oligonucleotide for the expected effect of suppressing p53 activity by inhibition. *Id.*

Appellants traverse. First, Appellants note that the combination of Smith with Soussi and Chopp cannot render claims 25 and 26 obvious. Those claims recite, respectively, a vector and a replication defective virus. These elements are absent from the Examiner's proposed combination of references.

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Second, Smith states that "[t]he present inventor has found that antisense p53 oligonucleotides can inhibit the proliferation of *and ultimately kill* primary human leukemic blasts while not producing similar effects on fresh normal bone marrow cells." Col. 6, lines 24-28 (emphasis added). According to Smith, his method may be used to "deplete the bone marrow of malignant cells prior to infusion back into the bone marrow donor." Abstract. Alternatively, antisense oligonucleotides may be administered systemically for anticancer therapy. *See id.*

There simply is no nexus between the methods disclosed by Smith and the methods encompassed by claims 22-26. Smith uses p53 antisense oligonucleotides to inhibit the proliferation of and ultimately kill transformed cells. In contrast, Appellants' methods use p53 antisense oligonucleotide *to prevent injured neurons from dying*. That is, the end result achieved by Smith is cell death, while the end result achieved by Appellants' methods is prevention of cell death. *See* Smith, col. 6, lines 49-55 ("since simple growth inhibition of malignant cells that lasts only during exposure to antisense oligonucleotides would not be adequate for systemic treatment, with respect to this aspect of the invention, it is particularly significant that the present inventor has been able to document selective killing of malignant cells").

Chopp does not provide the required nexus. As noted above, Chopp does not disclose either that p53 causes neuronal cell death in ischemic brain or that antagonizing the activity of p53 would prevent neuronal cell death in ischemic brain. Chopp simply reports that p53 levels are elevated in necrotic brain regions following ischemia. The Examiner has provided no basis for concluding that one of ordinary skill in the art would reasonably believe that Smith's method for using p53 antisense

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oligonucleotides to *kill* tumor cells could be used to *prevent the death* of ischemic neurons, even assuming *arguendo* that Chopp shows a role for increased p53 levels in neuronal cell death.

Lastly, Soussi does not provide the missing nexus. Soussi merely presents the nucleotide sequence of a cDNA encoding rat p53. Despite the Examiner's contrary assertion, Soussi does not render SEQ ID NO:1 obvious simply because this 18 nucleotide sequence is present in the 1627 nucleotide sequence reported by Soussi. There is nothing in Soussi that would lead one of ordinary skill in the art to choose this particular sequence fragment or to conclude that SEQ ID NO: 1 has any particular utility.

The combination of references would not motivate one of ordinary skill in the art to produce the claimed invention nor would there have been a reasonable expectation of success in using the claimed methods to inhibit toxicity in cultured neurons. Because none of the references relied on teach or suggest the claimed method, Appellants request the withdrawal of the rejection of claims 22-26 under 35 U.S.C. § 103(a).

If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

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Respectfully submitted,

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Dated: February 24, 2004

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APPENDIX

16. A recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, said recombinant virus comprising a nucleic acid selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

17. A recombinant virus according to claim 16, wherein said virus is an adenovirus.

18. A recombinant virus according to claim 16, wherein the nucleic acid comprises SEQ ID No. 2 or an active variant thereof.

19. A recombinant virus according to claim 16, wherein said virus comprises two nucleic acids selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

20. A recombinant virus according to claim 16, wherein said virus is a replication defective virus.

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21. A recombinant virus according to claim 16, wherein the nucleic acid encodes the p53Val135 mutated form of p53.

22. A method of inhibiting toxicity in cultured neuronal cells comprising administering to said cells a nucleic acid selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

23. The method according to claim 22, wherein the nucleic acid is a p53 antisense oligonucleotide.

24. The method of claim 23, wherein said oligonucleotide has the sequence of SEQ ID No. 1.

25. The method according to claim 22, wherein the nucleic acid is within a vector.

26. The method according to claim 25, wherein the vector is a replication defective virus.

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